## REMARKS

### Summary of the Invention

The invention features methods for assaying a compound for its ability to affect cell division by determining whether the compound affects the interaction between an isolated estrogen receptor beta (ERβ) polypeptide and mitosis arrest deficient 2 (MAD2), or a binding fragment thereof.

### The Office Action

Claims 1-3, 6, and 9-12 are pending. Claims 1-3, 6, and 9-12 are rejected under 35 U.S.C. § 112, first and second paragraph, for an inadequate written description and indefiniteness, respectively. Claims 1, 3, 6, 9, 10, and 12 are rejected under 35 U.S.C. § 102(b) for anticipation by Iafrati et al. (Nature Medicine 3:545-548, 1997; hereinafter "Iafrati"). Claims 9 and 10 are objected to for use of the undefined acronyms "ERβ", "MAD2", and "GST-ERβ". The amendment to the specification is objected to under 35 U.S.C. § 132 for introducing new matter. By this reply, Applicant cancels claims 9-12, and addresses each of the Examiner's rejections and objections below.

### Informalities

Claims 9 and 10 are objected to for reciting "ERβ", "MAD2", and "GST-ERβ" without defining the terms fully. Claims 9 and 10 have been cancelled. Therefore, this

objection should be withdrawn.

Objection to the Specification

The amendment to the specification and the amendment to the paper sequence listing filed in the reply to Office Action on September 26, 2002 are objected to under 35 U.S.C. § 132. The Examiner states that the amendments introduce new matter and must be cancelled. In response, Applicant respectfully requests that the amendment to the specification and the amendment to the paper sequence, both of which were provided in the reply to Office Action submitted on September 26, 2002, be withdrawn. This objection should now be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-3, 6, and 9-12 are rejected under 35 U.S.C. § 112, first paragraph, for an inadequate written description. The Examiner states:

> Claims 1, 9, and 10 recite terms "estrogen receptor beta", mitosis arrest deficient 2", "ER beta", "MAD2", or "GST-ERβ" which encompasses a variant protein because no structural limitations is provided...Applicant argue[s] that the functional properties of these polypeptides are clearly described in the specification. However, the terms are not limited by structure and the genus encompassed by the term is unlimited. *Eli Lilly* clearly indicated unreasonable genus limited by terms without structure is not patentable. *Eli Lilly* did not allow generic terms such as mammalian or vertebrate. (Office Action, p. 4.)

Furthermore, claim 10 is rejected under 35 U.S.C. § 112, first paragraph, for reciting new subject matter not disclosed in the specification as originally filed. Applicant respectfully disagrees. In the interest of advancing prosecution of the present claims, Applicant cancels claims 9-12 herewith. Therefore, the rejection of these claims should be withdrawn. The rejection is discussed below as it applies to claims 1-3 and 6.

The invention is based, at least in part, on the inventor's recognition that estrogen receptor beta (ERβ) and mitosis arrest deficient 2 (MAD2), both of which were well known in the art prior to the filing of the present application (see below), interact to affect cell division. Prior to the invention, no one had recognized this interaction or known that it could be used to identify agents that affect cell division. The present invention, therefore, is not the identification of these polypeptides or any specific structural variants thereof, but rather, the invention provides a method that uses these well known polypeptides, and the newly discovered interaction between them, to screen compounds for their ability to affect this interaction and thereby to affect cell division.

The M.P.E.P. § 2163.02 (Eighth Edition, August 2001) states:

> [A]n objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed."

In applying this standard, the Federal Circuit has held that the specification must convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. (*Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19

U.S.P.Q.2d 1111 (Fed. Cir. 1991)). As is discussed above, the invention features a method for screening compounds for their ability to affect the interaction between ERβ and MAD2. All that is required to practice the presently claimed method is an ERβ polypeptide, a MAD2 polypeptide, or a binding fragment thereof, and a test compound. Applicant was clearly in possession of this invention and conveyed it completely and accurately in the specification (see, e.g., page 6, line 7, through page 8, line 5).

The Examiner, citing *Regents of the University of California v. Eli Lilly and Co.* 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), concludes that the present specification does not provide a written description for the genus of variants of ERβ and MAD2 because the terms are not limited by structure and encompass unlimited species. The facts presented in *Lilly* and the present case are not equivalent. In *Lilly*, the Federal Circuit held that a claim to a genus (i.e., a vertebrate cDNA sequence encoding insulin) when only one species of that genus is described in the specification (i.e., the rat cDNA sequence encoding insulin) did not satisfy the written description requirements of 35 U.S.C. § 112, first paragraph. Furthermore, "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." (*Id*, at 1568.) In contrast to *Lilly*, the present claims are not directed to a "type of material generally known to exist", nor, in fact, to any material as in *Lilly*; the present claims are directed to a method that utilizes two well known and art-recognized polypeptides, ERβ and MAD2, and binding fragments of MAD2. These

polypeptides are not described for the first time in the present specification, as was the case for the insulin cDNA sequence in the patent at issue in *Lilly*. The structure (i.e., the nucleotide and amino acid sequence) and the function of ERβ and MAD2 polypeptides identified from several different organisms was well documented prior to the filing date of the present specification, and the terms ERβ and MAD2 in the present claims would adequately convey to the skilled artisan that these terms encompass those known polypeptides (see, e.g., ERβ: GENBANK accession numbers AJ000220 and NM_001437; and Mosselman *et al.*, FEBS Lett. 392:49-53, 1996, a copy of which is provided herewith, and Tremblay *et al* (Molecular Endocrinology 11:353-365, 1997, a copy of which was provided in the previous reply to Office Action; and MAD2: GENBANK accession numbers U72150, U14132, U83902, and U65410; and Li *et al.*, Science 274:246-248, 1996, a copy of which is provided herewith).

In addition, the M.P.E.P. § 2173.05(a) states:

> The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed. Applicants need not confine themselves to the terminology used in the prior art, but are required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained. During patent examination, the claims must be given the broadest reasonable interpretation consistent with the specification. (Citations omitted; emphasis added.)

The specification clearly states that the components of the presently claimed methods include ERβ and MAD2, or a binding fragment thereof. As is discussed above, several

prior art references confirm that the terms ERβ and MAD2 were well known by skilled artisans working within the field of cell biology, the field of the present invention. Therefore, based on the knowledge in the art, the terms ERβ and MAD2, in the absence of any additional structural detail, would be sufficient to establish the metes and bounds of these terms in the claims. Therefore, providing additional structural detail would be unnecessary (see, e.g., *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); "[a] patent need not teach, and preferably omits, what is well known in the art". Based on the foregoing remarks, Applicant respectfully requests that the rejection of claims 1-3, 6, and 9-12 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-3, 6, and 9-12 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Examiner states that "[c]laim 1, 9, and 10 recite terms 'estrogen receptor beta', 'mitosis arrest deficient 2', 'ER beta', 'MAD2', or 'GST-ERβ' which is amibiguous because it is not clear what is the metes and bounds of the terms which has no structural limitations." Applicant respectfully traverses this rejection.

The M.P.E.P. § 2173.05(a) states, *inter alia*, that "the meaning of every term used in a claim should be apparent from the prior art." As is discussed above, the prior art clearly recognizes the terms ERβ and MAD2. Therefore, these terms would be clearly understood by one skilled in the art without the need for additional structural limitations,

as is asserted by the Examiner. Accordingly, the rejection of claims 1-3, 6, and 9-12 should be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1, 3, 6, 9, 10, and 12 are rejected under 35 U.S.C. § 102(b) for anticipation by Iafrati. The Examiner asserts that Iafrati teaches all of the elements of present claims 1, 3, 6, 9, 10, and 12 because Iafrati discloses an effect on cell division when vascular cells, which express estrogen receptor beta, are treated with estradiol. The Examiner states that vascular cells inherently express MAD2. Applicant respectfully traverses this rejection and point out that claims 9-12 have been canceled.

Iafrati does not, expressly or inherently, teach all of the limitations of claims 1, 3, or 6. Iafrati describes the inhibitory effect of 17β-estradiol (E2) on vascular endothelial cell proliferation in an ERα knockout mouse model, as determined by a decrease in 5-bromo-2′-deoxyuridine (BrdU) labeling of the vascular endothelial cells (see, e.g., p. 545-546). Iafrati concludes that E2 suppresses vascular endothelial cell proliferation in the ERα knockout mouse; hypothesizing that the effect is mediated by ERβ (see, e.g., p. 547). Although Iafrati fails to teach or suggest the presence of MAD2, the Examiner asserts that vascular cells inherently express MAD2 and, furthermore, that Elledge (Science 249:999-1000, 1998) discloses that MAD2 is ubiquitous in cell division, thereby providing all of the elements of present claim 1. Contrary to the Examiner's conclusion,

Iafrati does not teach or suggest all of the limitations of present claim 1.

Claim 1 is directed to a method for determining whether a test compound is capable of affecting cell division, the first step of which involves contacting the test compound with isolated ERβ and MAD2, or a binding fragment thereof, under conditions in which ERβ and MAD2, or a fragment thereof, have formed or are able to form, a complex. The method then requires a second step of determining whether the test compound affects the ERβ/MAD2 complex or complex formation, a step which is absent in the Iafrati disclosure. Iafrati simply fails to teach or suggest the step of assaying whether the application of E2 to the injured carotid artery of an ERα knockout mouse has any effect on the ERβ/MAD2 complex or complex formation. Absent this disclosure, Iafrati fails to teach or suggest all of the limitations of present claim 1, and therefore, Iafrati cannot serve as the basis for a rejection of claims 1, 3, or 6, under 35 U.S.C. § 102(b) for anticipation. For this reason, Applicant respectfully requests that this rejection be withdrawn.

## CONCLUSION

Applicant submits that the claims are in condition for allowance, and such action is respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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